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(54) Title: USE OF SYNERGISTIC COMBINATIONS OF A NK_1 RECEPTOR ANTAGONIST AND A GABA ANALOG IN PSYCHIATRIC DISORDERS

(57) Abstract: The present invention provides methods of treatment using synergistic combinations of a NK_1 receptor antagonist and a GABA analog, and pharmaceutical compositions and products containing the NK_1 receptor antagonist and GABA analog. The present invention provides the use of a NK_1 receptor antagonist and a GABA analog for the manufacture of a medicament for the

compound, leading to a reduction in the side effects, and enhancement of the clinical utility of the compounds.

Accordingly, this invention provides a method for preventing or treating a psychiatric disorder comprising administering to a subject in need of treatment an amount of a synergistic combination of a NK_1 receptor antagonist and a GABA analog.

Preferably, the psychiatric disorder treated is anxiety, panic attack, generalized anxiety disorder, social phobia or depression.

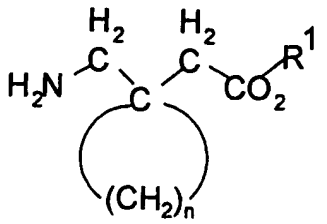
The invention also concerns the use of a composition comprising synergistic effective amounts of a NK_1 receptor antagonist and a GABA analog, or pharmaceutically acceptable salts thereof, for the preparation of a medicament useful for preventing or treating a psychiatric disorder.

BRIEF DESCRIPTION OF THE DRAWING

FIGURE 1. Dose response 30 min post drug for [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (CI-1021) in the isolation-induced vocalization model of anxiety in the guinea pig pup. Results are shown as mean % reduction ± SEM in the number of calls *vs.* baseline measurements taken before the treatment. *: $P<0.05$ *vs* vehicle group; #: $P<0.05$ *vs* their own vehicles (not included in the graph for clarity); Kruskall-Wallis test followed by Mann-Whitney test.

DETAILED DESCRIPTION OF THE INVENTION

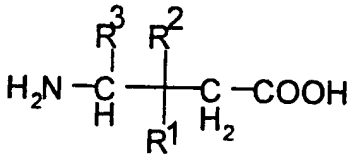
According to this invention, a NK_1 receptor antagonist is used in combination with a GABA analog to treat a psychiatric disorder in patients in need of such



(I)

wherein R^1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof. An especially preferred embodiment utilizes a GABA analog of Formula I where R^1 is hydrogen and n is 5, which compound is generically known as gabapentin. Other preferred GABA analogs have Formula I wherein the cyclic ring is substituted, for example with alkyl such as methyl or ethyl. Typical of such compounds include (1-aminomethyl-3-methylcyclohexyl) acetic acid, (1-aminomethyl-3-methylcyclopentyl) acetic acid and (1-aminomethyl-3-4-dimethylcyclopentyl) acetic acid.

In another embodiment, the method for preventing and treating a psychiatric disorder of the invention utilizes as a GABA analog a compound of Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R^2 is hydrogen or methyl; and

R^3 is hydrogen, methyl, or carboxyl. Diastereoisomers and enantiomers of compounds of Formula II can be utilized in the invention. An especially preferred method of the invention employs as GABA analog a compound of Formula II where R^2 and R^3 are both hydrogen, and R^1 is $-(CH_2)_{0-2}$-iC_4H_9 as an (R), (S), or (R,S) isomer. A more preferred embodiment of the invention employs, as GABA analog, 3-aminomethyl-5-methyl-hexanoic acid, and especially (S)-3-amino-methyl-5-methyl-hexanoic acid, known generically as pregabalin. Another preferred compound of Formula II is 3-(1-aminoethyl)-5-methyl-heptanoic acid.

The terms "patient" and "subject" are intended to include a mammal, especially a human.

The term "psychiatric disorder" is intended to include anxiety, panic attacks, generalized anxiety disorder, social phobia and depression.

All that is required to practice the method of preventing and treating a psychiatric disorder according to the present invention is to administer a synergistic NK_1-GABA analog combination in an amount that is effective to prevent or treat the disorder, i.e. to control the psychiatric disorder.

In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of a psychiatric disorder comprising the synergistic NK_1 antagonist - GABA analog combination. Formulating the active components of the combination in dosage unit form with at least one pharmaceutically acceptable carrier or excipient produces pharmaceutical formulations of the composition according to the present invention. For preparing pharmaceutical formulations from the compounds used in this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. They preferably contain 5% to about 70% of the active components of the combination. In such solid dosage forms, the active components are admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In

Examples of suitable liquid carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), and suitable mixtures thereof.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like can ensure prevention of the action of microorganisms. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active components of the combination. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms. Some examples of dosage unit forms are tablets, capsules, pills, powders, suppositories, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses.

The percentage of the active components in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10 % in a solid composition and at least 2 % in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active components is present, for example, from 10 % to 90 % by weight.

Routes of administration of the active components of the combination or their respective salts are parenteral or, preferably, oral. For example, a useful oral dosage is between 20 and 800 mg , expressed as the mass of the GABA analog, and a useful intravenous dose is between 5 and 50 mg. The dosage is within the dosing range used in treatment of a psychiatric disorder, or as would be dictated by the needs of the patient as described by the physician.

The ability of synergistic NK_1-receptor antagonist-GABA analog combinations to prevent or treat a psychiatric disorder has been established in several animal models.

EXAMPLE 1

Synergistic interaction between a NK_1-receptor antagonist and a GABA analog in isolation-induced vocalizations of guinea-pig pups

Methods:

Distress vocalizations of guinea-pig pups (2-14 days old) are quantified in a 5-min isolation period, after which they are reunited with their mothers and littermates. The test cage consists of a sound-attenuating box with a white interior and white illumination. The vocalizations are recorded by means of a microphone and a digital audio tape (DAT) recorder. Pups are first selected using the criterion of emitting a minimum of 500 vocalizations after three pre-tests on three consecutive days. On the day of the test, pups are submitted to a pre-treatment (baseline) measurement. Each pup then receives oral administration of test compounds and is returned to the home cage for 30 min before maternal separation.

Different ratios of combinations of doses are administered to groups of animals (n= 9-10 per group). A minimum of 3 total doses for each ratio of combination is examined. The difference in the number of calls emitted before and after treatment is counted using Spike2 software; percentage of reduction in the number of calls is analyzed using a Kruskall-Wallis test followed by Mann-Whitney test between vehicle and different treatments. For example, the oral administration of [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (0.01-10.0 mg/kg *p.o.*, in Gelucire™ vehicle 30 min before the test) dose-dependently blocked vocalizations with a MED of 1.0 mg/kg (Figure 6). With different ratios of combinations of doses of a NK_1 receptor antagonist and a GABA analog, a synergistic interaction is considered when a significant shift to the left from the additive line is achieved.

Sorbitol solution (70% N.F.)	40 mL
Sodium benzoate	20 mg
Saccharin	5 mg
Red dye	10 mg
Cherry flavor	20 mg
Distilled water q.s.	100 mL

The sorbitol solution is added to 40 mL of distilled water, and pregabalin and the benzofuranylmethyl ester are dissolved therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water.

EXAMPLE 4

Parenteral Solution

In a solution of 700 mL of propylene glycol and 200 mL of water for injection is added 0.5 g of [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)] and 10 g of pregabalin. The pH is adjusted to 6.5, and the volume is made up to 1000 mL with water for injection. The formulation is sterilized, filled into 5.0 mL ampoules each containing 2.0 mL, and sealed under nitrogen.

9. A method according to any one of claims 1 to 8 wherein the disorder treated is selected from anxiety, panic attacks, generalized anxiety disorder, social phobia or depression.

10. The use of a composition comprising synergistic amounts of a NK_1 receptor antagonist and a GABA analog effective in a psychiatric disorder, or pharmaceutically acceptable salts thereof, for the preparation of a medicament useful for preventing or treating a psychiatric disorder.

11. Use according to claim 10 characterized in that a psychiatric disorder is selected from anxiety, panic attacks, generalized anxiety disorder, social phobia and depression.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K31/404 A61K31/40 A61P25/18 A61P25/24
A61K45/06 //(A61K31/40,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 24439 A (ELLIOTT JASON MATTHEW ;HOLLINGWORTH GREGORY JOHN (GB); KULAGOWSKI) 11 June 1998 (1998-06-11) page 3, line 20 - line 27 page 6, line 21 -page 7, line 31 Assay 4 ---	1-11
Y	WO 98 15277 A (CARLSON EMMA JOANNE ;MERCK SHARP & DOHME (GB); RUPNIAK NADIA MELAN) 16 April 1998 (1998-04-16) page 3, line 27 -page 4, line 6 page 5, line 30 -page 6, line 10 Assay 2 ---	1-11
Y	US 5 510 381 A (PANDE ATUL C) 23 April 1996 (1996-04-23) column 1, line 46 -column 2, line 54 --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2001	07/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/10084

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The process for preparing a solid preparation of the 4-amino-3-substituted-butanoic acid derivative according to the invention as explained above comprises, for example, the granulation step in which a humectant, that is, a stabilizer, a binder and an auxiliary agent for manufacturing a pharmaceutical preparation are added to bulk powders of the said compound and then the resulting mixture is granulated by means of a granulator, the step for tableting in which additives such as a lubricant are added to the resulting granular powders and then the granules are compressed by means of a tableting machine and, if necessary, the coating step in which the surface of tablets obtained is coated. However, the granular powders as prepared by the granulation step may be applied as such in the dosage form of powders or granules as a pharmaceutical preparation of the 4-amino-3-substituted-butanoic acid derivative without conducting the tableting step, or the granules as prepared by the granulation step may be further subjected to the surface-coating step as described above. Alternatively, the granules as prepared by the granulation step may be admixed with a lubricant or the like and the resulting mixture may be filled into gelatin hard capsules by means of a capsule filler to prepare capsules. In the

The total amount to be used may be varied depending upon the sort of the humectant to be used, the specific dosage form of the solid composition containing the 4-amino-3-substituted-butanoic acid derivative, in other words, tablets, powders, granules or capsules, and also the sort and amount of an auxiliary to be added. The humectant should be used, in any case, in an effective amount to stabilize the 4-amino-3-substituted-butanoic acid derivative by ensuring a water retention of the pharmaceutical preparation. And, in many cases, a total amount of the humectant may be preferably in the range of 0.02 - 20% by weight relative to the 4-amino-3-substituted-butanoic acid derivative, or it may preferably be in the range of 0.02 - 20% by weight relative to the total amount of the 4-amino-3-substituted-butanoic acid derivative and an auxiliary agent when added for manufacturing a pharmaceutical preparation. However, when sorbitol is used together with other humectants, the amount to be used is not limited to the ranges as mentioned above.

In preparing surface-coated tablets of the 4-amino-3-substituted-butanoic acid derivative, the amount of the humectant to be used in the surface-coating step may be

disintegrator such as a cellulose derivative (e.g., hydroxypropylcellulose), crystalline cellulose, corn starch, partially gelatinized starch, lactose or the like or other conventional auxiliaries by means of a suitable mixer such as a dry mixer, e.g., a V-blender or the like and then the resulting mixture is compression-molded to tablets by means of a suitable tablet machine.

The granular powders, granules or tablets thus obtained may be surface-coated, if necessary. The surface-coating step for tablets is not essential and may be an optional step. For example, in case of gabapentin having a strongly bitter taste, it may be desirable to surface-coat gabapentin tablets for easier ingestion. In the surface-coating step, there may be used as a film-forming material a polymeric base ingredient such as a cellulose derivative, e.g., hydroxypropylcellulose (HPC), hydroxypropylmethyl-cellulose (HPMC), etc., a polyvinyl pyrrolidone, Kollidon-VA64, Eudragits, etc., and as a sweetening agent mannitol, sorbitol, xylitol, aspartame and the like.

To such a film-forming material, there may be further added, if necessary, a humectant such as propylene glycol, glycerol, triacetin or the like and a neutral amino acid such as L-leucine, L-isoleucine, L-valine, L-alanine,

Kollidon-K25), a copolyvidone (e.g., Kollidon-VA64) and the like in the form of a solution or suspension thereof.

The aforementioned stabilizer solution may be applied to bulk powders of the 4-amino-3-substituted-butanoic acid derivative prior to the granulation using the binder or other auxiliaries for manufacturing a pharmaceutical preparation. In this granulation step, there may be also incorporated, if necessary, a sweetening agent such as mannitol, sorbitol, xylitol or the like and other auxiliaries for manufacturing a pharmaceutical preparation.

The granular powders thus obtained may be used as a pharmaceutical preparation of the 4-amino-3-substituted-butanoic acid derivative as such, or they may be also encapsulated under compression for capsules containing the 4-amino-3-substituted-butanoic acid derivative. Also, they may be further compressed to tablets.

More specifically, the granular powders of the 4-amino-3-substituted-butanoic acid derivative obtained as described above can be compression-molded to tablets by means of a tablet machine. It is essential in this compression-molding step to use a lubricant as ordinarily done for the manufacture of a pharmaceutical preparation. However, it has been discovered that some conventional

chain aliphatic acid polyglycerol ester such as monolauric acid polyglyceride or monomyristic acid polyglyceride and the like.

The solid pharmaceutical preparation of the present invention can be obtained in a usual dosage form, typically, in the dosage form of powders, granules, surface-coated granules, capsules, tablets or surface-coated tablets by conducting in turn the granulation step in which a humectant as a stabilizer and, if necessary, an auxiliary agent for manufacturing a pharmaceutical preparation are added to bulk powders of a 4-amino-3-substituted-butanoic acid derivative, such as gabapentin, pregabalin, baclofen and the like and the resulting mixture is granulated by means of a granulator, the encapsulation step in which the resulting granular powders are encapsulated under compression by means of a capsule filler or the tableting step in which the resulting granular powders are compressed by means of a tablet machine and, if necessary, the coating step in which the granular powders, tablets or granules obtained in the preceding steps are surface-coated.

The granulation of the 4-amino-3-substituted-butanoic acid derivative during the process for manufacturing pharmaceutical preparations as stated above

Table 2 (Cont'd)

$NH_2CH_2-C(R_1)(R_2)-CH_2COOH$

>C<R₁,R₂	>C<R₁,R₂